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Regular Article

TRANSPLANTATION

Common hereditary variants of the *APOE* gene and posttransplant outcome in acute myeloid leukemia

Julian Ronnacker,[1] Michael Grau,[1] Maximilian Klasmeier,[1] Christian Klesse,[2] Henning Baldauf,[2] Stefan Abert,[2] Andrew F. Berdel,[1] Friederike T. Füsser,[3] Sarah Sandmann,[4] Jörn Albring,[1] Christian Reicherts,[1] Simon Call,[1] Julia Marx,[1] Matthias Floeth,[1] Eva Eßeling,[1] Lina Kolloch,[1] Philipp Berning,[1] Annika Scheller,[1] Klaus Wethmar,[1] Hartmut Schmidt,[5] Bernhard Schlüter,[5] Wolfgang E. Berdel,[1] Benjamin N. Ostendorf,[6,7] Sohail F. Tavazoie,[8] Jan-Henrik Mikesch,[1] Georg Lenz,[1] Katharina Fleischhauer,[9] Johannes Schetelig,[2,10] Matthias Stelljes,[1] and Christoph Schliemann[1]

[1]Department of Medicine A, University Hospital Münster, Münster, Germany; [2]Collaborative Biobank, DKMS Group gGmbH, Tübingen, Germany; [3]Institute for Pharmaceutical and Medical Chemistry and [4]Institute of Medical Informatics, University of Münster, Münster, Germany; [5]Center for Laboratory Medicine, University Hospital Münster, Münster, Germany; [6]Department of Hematology, Oncology, and Tumor Immunology, Berlin Institute of Health, Charité Universitätsmedizin Berlin, Berlin, Germany; [7]Berlin Institute for Medical Systems Biology, Max Delbrück Center for Molecular Medicine, Berlin, Germany; [8]Laboratory of Systems Cancer Biology, The Rockefeller University, New York, NY; [9]Institute for Experimental Cellular Therapy, University Hospital Essen, Essen, Germany; and [10]Department of Medicine I, University Hospital Dresden, Dresden, Germany

KEY POINTS

- **Patients with acute myeloid leukemia who carry an *APOE2* allele have inferior survival after allogeneic transplantation.**
- **The *APOE2* allele is associated with an increased risk of acute and chronic GVHD when present in the host or transferred from the donor.**

Apolipoprotein E (APOE) has multiple functions in metabolism and immunoregulation. Its common germ line variants *APOE2*, *APOE3*, and *APOE4* give rise to 3 functionally distinct gene products. Previous studies reported yin-yang roles of *APOE2* and *APOE4* in immunological processes, but their effects in hematopoietic stem cell transplantation (HSCT) have never been studied. We performed *APOE* genotyping in 2 contemporary cohorts of 348 and 447 patients with acute myeloid leukemia who had received allogeneic HSCT and evaluated the associations of recipient and donor *APOE* genetic variations with posttransplant outcomes. Patients who carried at least 1 *APOE2* allele had a higher risk of posttransplant death than *APOE4* carriers in the discovery (hazard ratio [HR], 2.09; *P* = .024) and validation cohorts (HR, 1.96; *P* = .040). Detrimental *APOE2* effects were driven by an increased risk of severe chronic graft-versus-host disease (GVHD; adjusted HR [HR_{adj}], 1.85; *P* = .034) and nonrelapse death (HR_{adj}, 1.72; *P* = .044). In non-*APOE2* recipients, transplantation of an *APOE2*-positive allograft was associated with an increased incidence of grade 3 to 4 acute GVHD (HR_{adj}, 2.82; *P* = .012) and severe chronic GVHD (HR_{adj}, 2.54; *P* = .022) compared with *APOE2*-negative grafts. In summary, the *APOE2* allele, typically considered a longevity gene in the general population, was associated with a higher risk of acute GVHD (HR_{adj}, 2.75; *P* = .002), chronic GVHD (HR_{adj}, 2.57; *P* = .001), and posttransplant mortality (HR_{adj}, 1.79; *P* = .004), when present in either the host or transplanted from the donor.

Introduction

Apolipoprotein E (APOE), in addition to its canonical functions in lipid metabolism, modulates several inflammation-related pathophysiological processes, including atherosclerosis, neurodegeneration, infection, and antitumor immunity.[1-6] In humans, the *APOE* gene locus, located on chromosome 19q13.32, carries 2 single-nucleotide polymorphisms (SNPs) at rs429358 and rs7412, which result in 3 highly prevalent genetic variants (Figure 1A): *APOE2* (frequency, 10%-15%), *APOE3* (60%-70%; the reference allele present in the majority of the population), and *APOE4* (15%-20%).[7-9] Within the general global population, allele frequencies vary across geographical, racial, and ethnic groups.[10-13] For example, *APOE2* and *APOE4* alleles are more prevalent in African Americans than in White peoples,[7,14] whereas *APOE2* is almost absent in Native American populations.[10] Interestingly, the allele frequency of *APOE4* gradually increases with latitude in North America and Eurasia.[11] In Europe, *APOE4* frequencies range from 5% to 6% in southern Italy to 23% in Finland, whereas *APOE3* follows an opposite trend, and *APOE2* frequencies are relatively stable.[11] Although the encoded isoforms differ by only 1 or 2 amino acids, these changes have profound effects on their structure, activation of APOE receptors, and functional properties, even resulting in orthogonal biological effects.[5,15,16] As an example, although *APOE4* is a major risk factor for the onset and progression of Alzheimer dementia and other neurodegenerative diseases,[1,17-19] *APOE2* is protective and associated with a

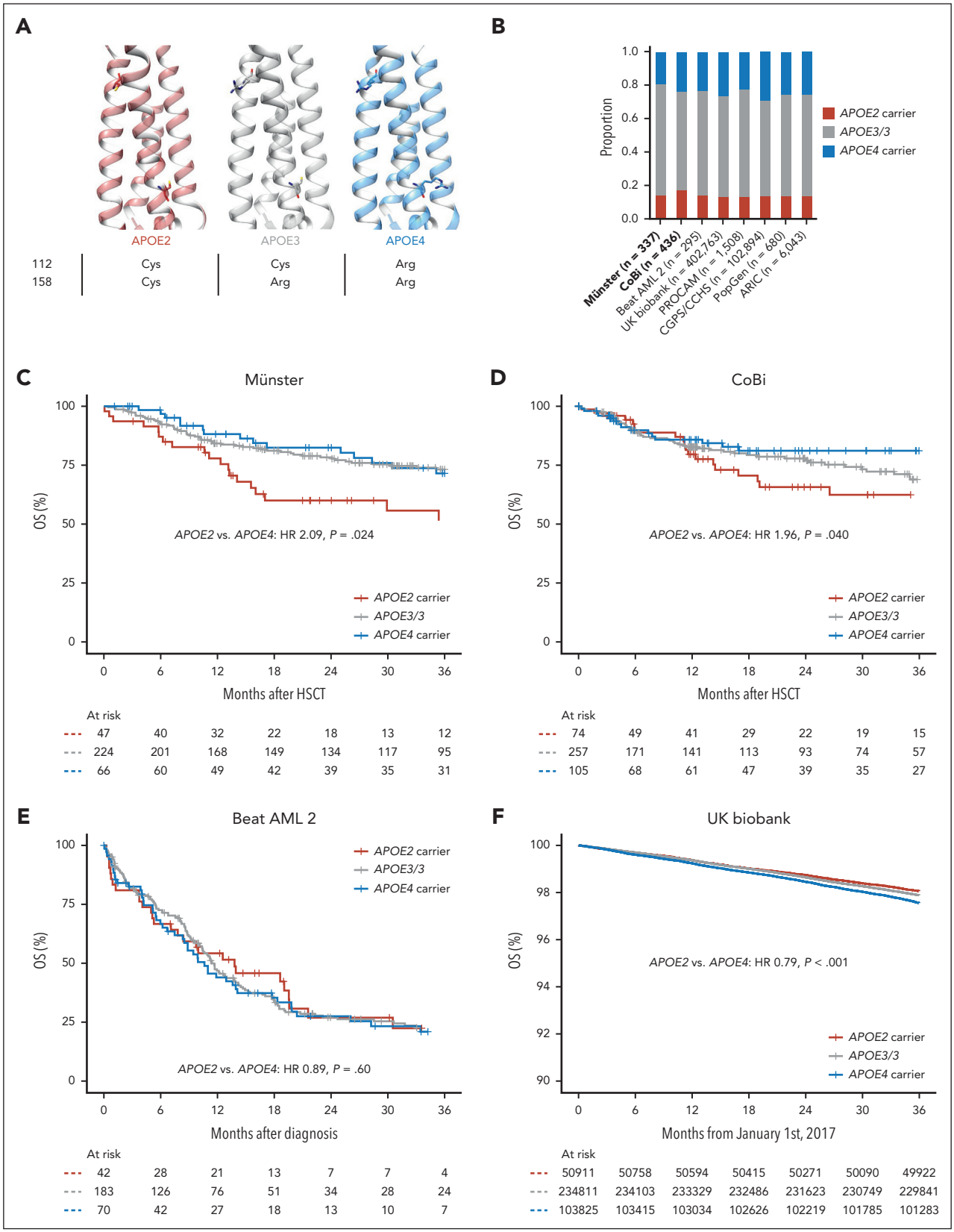

Figure 1. Recipient *APOE* carrier status and posttransplant survival in patients with AML. (A) Schematic representation of the 3 hereditary isoforms APOE2, APOE3, and APOE4, rendered using ChimeraX.[23] (B) Distribution of *APOE* carrier status in the Münster and CoBi cohorts, compared with patients with AML without HSCT from Beat AML 2 and previously published general population epidemiologic cohorts.[7-9,13] Cohorts genotyped in this work are marked in bold. (C) Kaplan-Meier estimates for OS by *APOE* carrier status in transplant recipients in the Münster discovery cohort. (D) Kaplan-Meier estimates for OS by *APOE* carrier status in transplant recipients in the CoBi validation cohort. (E) Kaplan-Meier estimates for OS by *APOE* carrier status in patients with AML who did not receive transplant from the Beat AML project. (F) Kaplan-Meier estimates for

reduced risk of cognitive impairment and increased longevity.[20-22]

More recently, *APOE* variants have been shown to play a critical role in antitumor immunity.[4,24,25] Cellular mediators of APOE effects include myeloid-derived suppressor cells, dendritic cells, monocytes, macrophages, and T cells.[4,5,26,27] In melanoma, individuals who carried at least 1 *APOE4* allele showed reduced tumor progression and prolonged survival compared with *APOE2* carriers under immune checkpoint blockade, suggesting opposing effects of *APOE2* and *APOE4* in cancer immunotherapy.[5] In COVID-19, the *APOE2* variant was associated with proinflammatory signaling, whereas *APOE4* was associated with reduced immune activation and delayed antiviral activity upon initial infection but robust antiviral T-cell immunity at later disease stages.[6]

Inspired by the emerging functions of *APOE* and its variants in modulating immunity, we sought to investigate the impact of *APOE* germ line variation in the context of allogeneic hematopoietic stem cell transplantation (HSCT), one of the oldest forms of cancer immunotherapy,[28] whose success critically depends on a balanced titration of immune reactions. To this end, we genotyped *APOE* polymorphisms in 795 patients with acute myeloid leukemia (AML) from 2 contemporary cohorts who underwent HSCT. The fact that APOE, although primarily synthesized in the liver,[29] is also expressed in monocytes, macrophages, dendritic cells, and neutrophils,[26,30,31] and that hematopoietic-derived APOE modifies inflammatory processes in a genotype-dependent fashion,[5,32,33] allowed for us to address both the effects of the *APOE* genotype of the stem cell recipient and the donor.

Patients and methods

Study population

In this retrospective study, we analyzed *APOE* germ line variation in 2 large cohorts of adult patients with AML aged ≥18 years who underwent a first allogeneic HSCT in hematological remission. The initial discovery cohort consisted of 348 patients who underwent transplant at the University Hospital Münster, Germany, between 2014 and 2024. Clinical data were retrieved from electronic medical records. Genomic DNA isolated from peripheral blood mononuclear cells and biobanked as part of clinical routine was used for *APOE* genotyping. Corresponding donor DNA was available for 330 patients. An exploratory immune subpopulation analysis by *APOE* status included all patients with available data, and patients with relapse or graft-versus-host disease (GVHD) were not excluded. The study was approved by the Ethics Committee Westphalia-Lippe (2023-032-f-S) as well as by the Scientific Committee of the Collaborative Biobank.

The validation cohort consisted of 447 patients with AML who were prospectively enrolled from 7 centers to the German Collaborative Biobank (CoBi) between 2017 and 2023. CoBi is a nonprofit multicenter registry of German stem cell transplantation and collection centers and has been approved by the Ethics Committee in Dresden (EK 159042016). All patients have provided signed informed consent for longitudinal deidentified clinical data storage and DNA biobanking from whole blood samples. Donor DNA was available for 153 patients. Transplant recipients who were enrolled in the CoBi registry at the University Hospital Münster were excluded from the CoBi data set.

APOE genotyping

APOE genotyping was performed on genomic DNA using a Taqman-based qualitative real-time polymerase chain reaction for positions 112 (rs429358) and 158 (rs7412). Detailed information is provided in supplemental Methods, available on the *Blood* website. For analysis of the Beat AML 2 cohort,[34] based on granted access to the database of genotypes and phenotypes-controlled part of the Beat AML project (phs001657.v2.p1), we extracted *APOE* SNPs from whole-exome data, as described in supplemental Methods. For the UK Biobank general population cohort,[35] *APOE* genotyping results, clinical data, and survival data were downloaded from the respective data portal on 22 June 2021. Across all cohorts, individuals who were heterozygous or homozygous for *APOE2* or *APOE4* were grouped together as *APOE2* or *APOE4* carriers, respectively, as previously done,[5,36] and individuals with the rare *APOE4/2* genotype were excluded because of ambiguous and possibly opposing biological effects and small numbers.[5,6]

Outcomes and biostatistical analysis

The study was focused on the analysis of the *APOE* gene alone, based on its biological functions reported in immune-related diseases, and was not part of a larger genome-wide association study. Clinical baseline characteristics were compared using the χ^2 or the Fisher exact test for categorical variables and the Mann-Whitney *U* test or the Kruskal-Wallis test for continuous variables. The primary end point was overall survival (OS). Secondary end points were exploratory and included grade 3 to 4 acute GVHD, severe chronic GVHD, nonrelapse mortality (NRM), relapse, and GVHD- and relapse-free survival (GRFS) by recipient and donor *APOE* genotype. Time-to-event variables were calculated from the day of HSCT and were estimated using the Kaplan-Meier or the Aalen-Johansen method. OS was defined as the time from the date of HSCT to death from any cause. Death without AML relapse was regarded as a competing risk for estimating the cumulative incidence of relapse, and relapse was regarded as a competing risk for estimating the probability of NRM. Relapse and death without GVHD were competing risks for GVHD. GRFS was defined as the time to grade 3 to 4 acute GVHD, severe chronic GVHD, AML relapse, or death, whichever occurred first. Acute GVHD was graded according to Harris et al,[37] and chronic GVHD was graded according to Jagasia et al.[38] Primary causes of death were defined according to previously published definitions.[39]

Cox regression was used to examine the association of host or donor *APOE* germ line variation with the hazard of an event in the presence of potential confounders. Fine-Gray regression

Figure 1 (continued) OS by *APOE* carrier status in UK Biobank participants over a 3-year observation period from 1 January 2017. Data were censored on 31 December 2019. Survival of UK Biobank participants from April 2019 to March 2021, encompassing in part the COVID-19 pandemic, is shown in supplemental Figure 2. ARIC, Atherosclerosis Risk in Communities Study; CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; PROCAM, Prospective Cardiovascular Münster Study.

Table 1. Patient, disease, and transplant characteristics of the Münster discovery cohort by *APOE* carrier status

	All patients (n = 337)	*APOE2* carriers (n = 47)	*APOE3/3* (n = 224)	*APOE4* carriers (n = 66)	*P* value
Age, y, median (range)	59 (20-75)	57 (21-74)	59 (20-75)	59 (20-75)	.90*
Sex, n (%)					.76†
Male	200 (59)	27 (57)	136 (61)	37 (56)	
Female	137 (41)	20 (43)	88 (39)	29 (44)	
Ethnicity, n (%)					.26‡
European White	325 (96)	47 (100)	216 (96)	62 (94)	
Other	12 (4)	0 (0)	8 (4)	4 (6)	
ELN 2017 genetic risk, n (%)					.80†
Favorable	90 (27)	15 (32)	60 (27)	15 (23)	
Intermediate	116 (34)	16 (34)	78 (35)	22 (33)	
Adverse	131 (39)	16 (34)	86 (38)	29 (44)	
Pretransplant remission status, n (%)					.61†
CR	265 (79)	37 (79)	179 (80)	49 (74)	
CRi	72 (21)	10 (21)	45 (20)	17 (26)	
HCT-CI, median (range), points	2 (0-9)	2 (0-9)	1 (0-9)	2 (0-7)	.35*
Recipient/donor HLA match, n (%)					.99‡
10/10 matched, unrelated	201 (60)	30 (64)	131 (58)	40 (61)	
10/10 matched, related	93 (28)	12 (26)	62 (28)	19 (29)	
<10/10 matched, unrelated	33 (10)	4 (9)	24 (11)	5 (8)	
Haploidentical	10 (3)	1 (2)	7 (3)	2 (3)	
Recipient/donor sex match, n (%)					.99†
Female donor/male recipient	44 (13)	6 (13)	29 (13)	9 (14)	
All others	293 (87)	41 (87)	195 (87)	57 (86)	
CMV risk, n (%)					.91†
Standard risk	124 (37)	16 (34)	83 (37)	25 (38)	
Seropositive recipient	213 (63)	31 (66)	141 (63)	41 (62)	
Conditioning intensity, n (%)					.23‡
NMA	5 (1)	2 (4)	3 (1)	0 (0)	
RIC	173 (51)	19 (40)	120 (54)	34 (52)	
MAC	159 (47)	26 (55)	101 (45)	32 (48)	
Stem cell source, n (%)					1.00‡
PBSC	331 (98)	46 (98)	221 (99)	64 (97)	
BM	6 (2)	1 (2)	3 (1)	2 (3)	
Transplantation period, n (%)					.64†
2014-2019	162 (48)	20 (43)	108 (48)	34 (52)	
2020-2024	175 (52)	27 (57)	116 (52)	32 (48)	

P values describe the heterogeneity of baseline variables among *APOE2* carriers, *APOE3* homozygotes, and *APOE4* carriers. Missing/incomplete observations were not included in group comparisons.

ATG, antithymocyte globulin; BM, bone marrow; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CR, complete remission; CRi, CR with incomplete recovery; ELN, European LeukemiaNet; MAC, myeloablative conditioning; MMF, mycophenolate mofetil; MTX, methotrexate; NMA, nonmyeloablative conditioning; PBSC, peripheral blood hematopoietic stem cells; PTCY, posttransplant cyclophosphamide; RIC, reduced-intensity conditioning.

*Kruskal-Wallis test.

†χ^2 test.

‡Fisher exact test.

Table 1 (continued)

	All patients (n = 337)	*APOE2* carriers (n = 47)	*APOE3/3* (n = 224)	*APOE4* carriers (n = 66)	*P* value
ATG-based conditioning, n (%)					.81†
Yes	229 (68)	32 (68)	150 (67)	47 (71)	
No	108 (32)	15 (32)	74 (33)	19 (29)	
Posttransplant immunosuppression, n (%)					.30‡
CNI/MTX	241 (72)	29 (62)	163 (73)	49 (74)	
CNI/MMF	65 (19)	14 (30)	38 (17)	13 (20)	
CNI/PTCY/MMF	31 (9)	4 (9)	23 (10)	4 (6)	

P values describe the heterogeneity of baseline variables among *APOE2* carriers, *APOE3* homozygotes, and *APOE4* carriers. Missing/incomplete observations were not included in group comparisons.

ATG, antithymocyte globulin; BM, bone marrow; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CR, complete remission; CRi, CR with incomplete recovery; ELN, European LeukemiaNet; MAC, myeloablative conditioning; MMF, mycophenolate mofetil; MTX, methotrexate; NMA, nonmyeloablative conditioning; PBSC, peripheral blood hematopoietic stem cells; PTCY, posttransplant cyclophosphamide; RIC, reduced-intensity conditioning.

*Kruskal-Wallis test.

†χ^2 test.

‡Fisher exact test.

models[40] were used for multivariable modeling of competing risk end points. Variable selection was guided by clinically established risk factors associated with posttransplant complications and outcomes. The heterogeneity of *APOE* genotype effects among subgroups was assessed by test for interaction. The multitree-based machine learning algorithm *XGBoost* was used to understand the relative importance of *APOE* variants among other clinical baseline variables, with the *SHAP* framework (SHapley Additive exPlanations; R package *SHAPforxgboost*) used to postprocess the model results and to rank potential risk factors.

The NetMHCpan algorithm[41,42] was used to predict HLA class I binding affinities of potential peptides (8- to 11-mers) encompassing the non-synonymous SNPs at rs7412 in graft-versus-host (GvH) direction against the 7 most common *HLA* class I alleles in the German population,[43] as described in supplemental Methods.

Statistical analyses and visualization were performed with R (version 2023.12.1) and GraphPad Prism (version 10.2.3). Two-sided *P* values <.05 were considered to indicate statistically significant differences.

Results

APOE allelic distribution and recipient characteristics

Patient flow is depicted in supplemental Figure 1, and *APOE* genotyping results are provided in supplemental Table 1. Baseline and transplant characteristics of the 337 transplant recipients in the final Münster discovery set are listed in Table 1. Of the 337 patients, 47 (14%) carried at least 1 *APOE2* allele (ie, were heterozygous or homozygous), 224 (66%) were *APOE3* homozygous (*APOE3/3*), and 66 (20%) carried at least 1 *APOE4* allele. This distribution did not deviate from the Hardy-Weinberg equilibrium (*P* = .50; χ^2 test), and the *APOE* allele frequencies were consistent with the frequencies in previously published epidemiologic studies, including the Prospective Cardiovascular Münster study[8] from the same region (Figure 1B). *APOE2* carriers, *APOE3* homozygotes, and *APOE4* carriers were similar with respect to age, sex, European LeukemiaNet 2017 genetic risk, pretransplant remission status, hematopoietic cell transplantation comorbidity index (HCT-CI) scores, recipient/donor HLA and sex match, cytomegalovirus (CMV) serostatus, antithymocyte globulin (ATG) treatment, conditioning intensity, stem cell source, transplantation period, and posttransplant immunosuppression (Table 1).

In the CoBi validation cohort, the frequencies of *APOE2* carriers, *APOE3* homozygotes, and *APOE4* carriers were 17% (74/436), 59% (257/436), and 24% (105/436), with no deviation from the Hardy-Weinberg equilibrium (*P* = .57; χ^2 test). Clinical characteristics were not different among the 3 *APOE* genotypic groups (supplemental Table 2).

Recipient *APOE* genotype and overall posttransplant mortality

We first examined the effect of recipient *APOE* genetic variation on survival after HSCT. In the Münster cohort, the median follow-up was 3.5 years (range, 0-8.9), and the estimated 3-year OS was 70% (95% confidence interval [CI], 65-76). We found a significantly higher risk of posttransplant death among patients with AML who carried at least 1 *APOE2* allele than those who carried at least 1 *APOE4* allele (hazard ratio [HR], 2.09; 95% CI, 1.10-3.97; *P* = .024) or were *APOE3* homozygotes (HR, 1.95; 95% CI, 1.19-3.20; *P* = .008; Figure 1C). In contrast, we did not detect differences in survival between *APOE4* carriers and *APOE3/3* homozygotes (HR, 0.93; 95% CI, 0.55-1.60; *P* = .80). In the CoBi cohort, the median follow-up was shorter at 1.9 years (range, 0-6.3), and the estimated 3-year OS was 71% (95% CI, 65-77). Similar to the discovery cohort, *APOE2*-positive transplant recipients exhibited significantly shorter OS than *APOE4* carriers (HR, 1.96; 95% CI, 1.03-3.74; *P* = .040; Figure 1D), whereas posttransplant survival did not differ between *APOE4* carriers and *APOE3* homozygous individuals (HR, 0.70; 95% CI, 0.40-1.21; *P* = .20).

We hypothesized that *APOE* germ line effects on survival were linked to the allogeneic HSCT procedure and leveraged whole-exome sequencing data from the Beat AML 2 database to analyze *APOE* genotypic effects in patients with AML who did not receive transplant (supplemental Figure 2). Notably, survival in the 295 individuals who never underwent transplantion was similar among *APOE2* carriers, *APOE3* homozygotes, and *APOE4* carriers, and no adverse *APOE2* effects were observed (*APOE2* vs *APOE4*; HR, 0.89; 95% CI, 0.56-1.40; $P = .60$; Figure 1E). Conversely, among participants from the general population participating in the UK Biobank, *APOE2* carrier status was associated with a significantly reduced risk of death over 3 years of observation, compared with *APOE4* carriers and *APOE3/3* homozygous individuals (*APOE2* vs *APOE4*: HR, 0.79; 95% CI, 0.74-0.85; $P < .001$; *APOE2* vs *APOE3/3*: HR, 0.92; 95% CI, 0.86-0.98; $P = .012$), both in a prepandemic period (January 2017 to December 2019; n = 389 547; Figure 1F) and in a period encompassing in part the severe acute respiratory syndrome coronavirus 2 pandemic (April 2019 to March 2021; n = 386 186; supplemental Figure 3). In the transplant cohorts, we found no interaction between *APOE* genotype and risk of death by prepandemic and intrapandemic/postpandemic time of HSCT ($P_{interaction} = .41$; supplemental Figure 4).

Taken together, these findings suggested that in patients with AML, common hereditary variants of *APOE* affect outcomes specifically in the setting of allogeneic HSCT. The observation that *APOE2* associates with a higher risk of posttransplant death was particularly surprising, given its association with an increased life span in the general population.

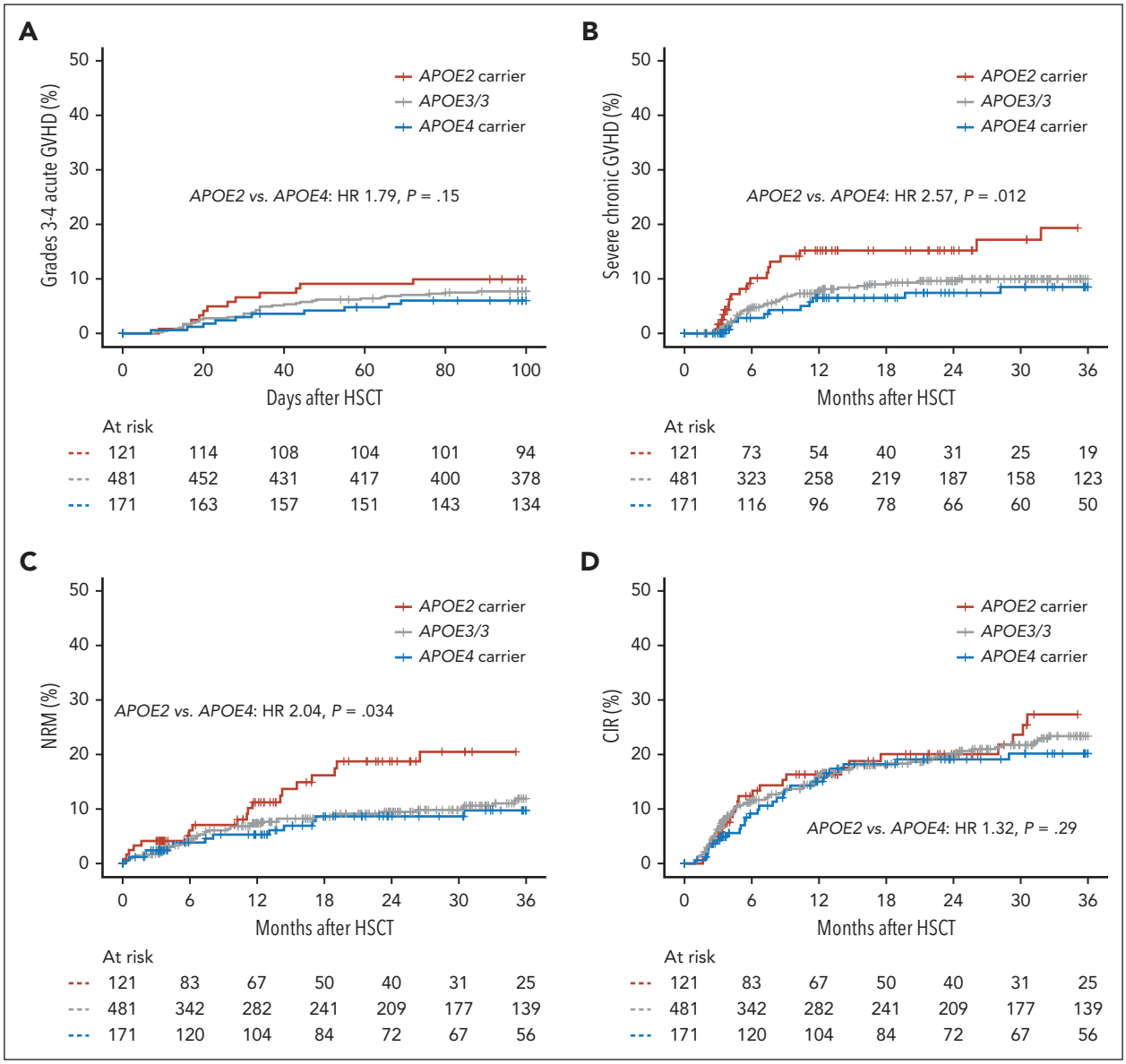

Figure 2. *APOE* germ line variation and posttransplant complications in patients with AML. (A-B) Cumulative incidences of grade 3 to 4 acute GVHD (A) and severe chronic GVHD (B), adjusted for relapse and death without GVHD, by *APOE* carrier status in patients with AML receiving allogeneic HSCT in the merged cohorts. (C-D) Cumulative incidences of NRM (C) and relapse (D) by *APOE* carrier status.

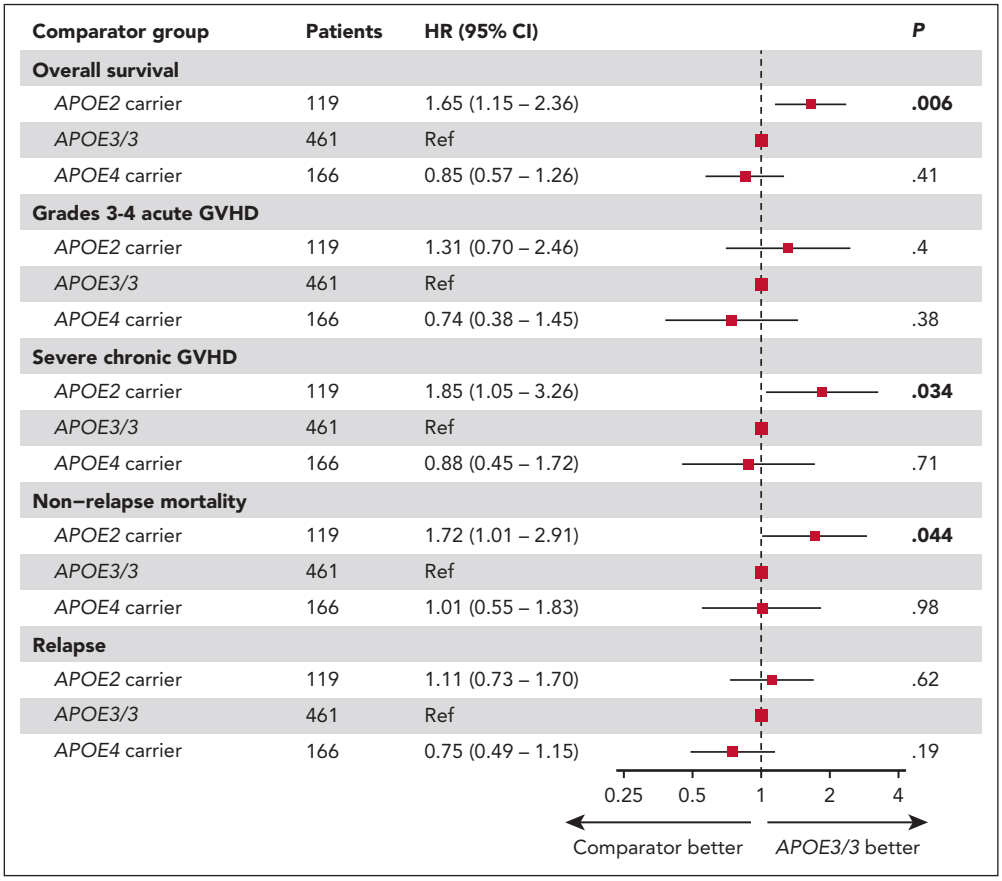

Figure 3. Forest plot of multivariable adjusted risks of primary and secondary end points by recipient *APOE* carrier status. Adjustments were made for patient age, ELN 2017 genetic risk, HCT-CI scores, pretransplant remission status, ATG treatment, conditioning intensity, recipient/donor HLA match, and recipient/donor sex match. Ref, reference.

Drivers of recipient *APOE* genotype effects on posttransplant outcome

To further dissect the drivers of adverse *APOE2* effects, we analyzed competing risk end points using both the discovery and validation cohorts combined as a single cohort to maximize the available sample size (supplemental Table 3). The cumulative incidence of grade 3 to 4 acute GVHD was nonsignificantly increased in *APOE2* carriers (*APOE2* vs *APOE4*: HR, 1.79; 95% CI, 0.81-3.95; $P = .15$; Figure 2A), and the risk of severe chronic GVHD was increased among *APOE2* carriers relative to *APOE4* carriers or *APOE3* homozygotes (*APOE2* vs *APOE4*: HR, 2.57; 95% CI, 1.23-5.38; $P = .012$; *APOE2* vs *APOE3/3*: HR, 1.97; 95% CI, 1.14-3.40; $P = .015$; Figure 2B). *APOE2* carriers also had a higher risk of death without AML relapse (*APOE2* vs *APOE4*: HR, 2.04; 95% CI, 1.06-3.94; $P = .034$; Figure 2C), whereas relapse risk was not different (*APOE2* vs *APOE4*: HR, 1.32; 95% CI, 0.78-2.23; $P = .29$; Figure 2D). Notably, trends toward increased NRM and severe chronic GVHD incidence were observed independently in the 2 cohorts (supplemental Figure 5). The distribution of causes of death showed no significant differences between *APOE2*, *APOE3*, and *APOE4* carriers (supplemental Table 4). However, preceding grade 3 to 4 acute or severe chronic GVHD was observed in 7 of 21 *APOE2* carriers (33%), 5 of 63 *APOE3* homozygotes (8%), and 2 of 17 *APOE4* carriers (12%) who succumbed to relapse.

The adverse effects of the *APOE2* allele on posttransplant OS, chronic GVHD, and NRM were confirmed after adjusting for age, AML genetic risk, HCT-CI, pretransplant remission status, ATG treatment, conditioning intensity, and recipient/donor HLA and sex match (Figure 3; supplemental Table 5). Additional risk factors included older age (for OS and NRM), adverse genetic risk (for OS and relapse), high HCT-CI (for NRM), and non-ATG conditioning and male recipient/female donor sex mismatch (for severe chronic GVHD). No significant interaction of baseline or transplant variables with *APOE2* effects was observed with respect to OS (supplemental Figure 4).

When analyzing global parameters of posttransplant immune reconstitution, no differences in humoral or cellular recovery after HSCT were observed between the 3 genotypic groups (supplemental Figures 6-7).

Donor *APOE* germ line variation and posttransplant outcomes

In addition to the liver, the hematopoietic compartment has been shown to produce APOE in humans. Therefore, we asked whether donor *APOE* genotype might also affect posttransplant outcomes and investigated this in an exploratory analysis of 452 recipients from both cohorts for whom corresponding donor DNA was available (supplemental Figure 1). Clinical characteristics of patients who received transplant from *APOE2*, *APOE3/*

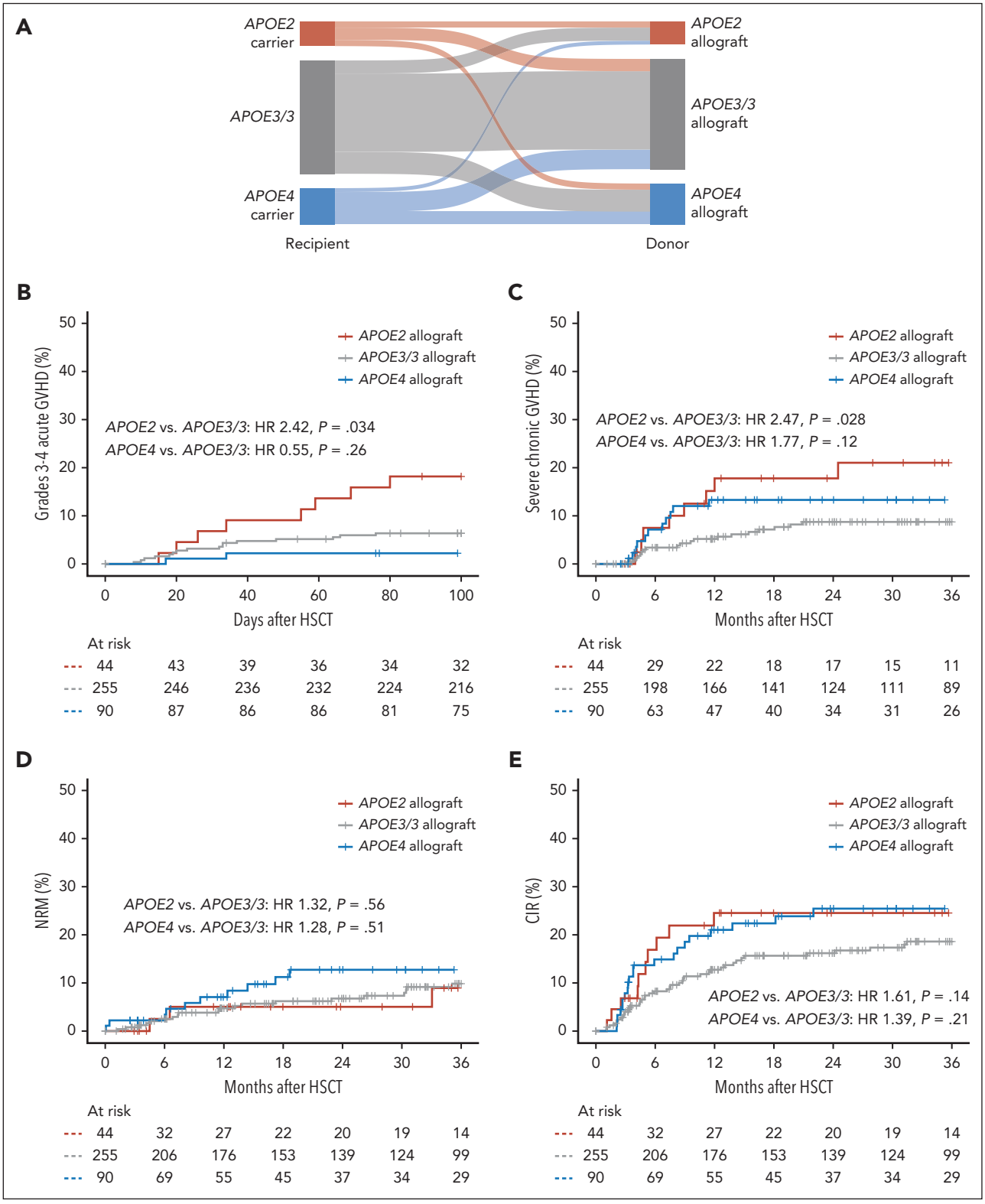

Figure 4. Posttransplant complications in *APOE2* noncarriers by donor *APOE* status. (A) Sankey diagram depicting the distribution of recipient and donor *APOE* status. (B-C) Cumulative incidences of grade 3 to 4 acute GVHD (B) and severe chronic GVHD (C) by donor *APOE* status. (D-E) Incidences of NRM (D) and relapse (E) by donor *APOE* status.

3, or *APOE4* donors were similar (supplemental Table 6). Of 452 patients, 59 (13%) received allografts from *APOE2*-carrying donors, 287 (63%) received *APOE3/3* allografts, and 106 (23%) received allografts from *APOE4*-carrying donors. A nonrandom higher probability of receiving an *APOE* carrier status–concordant allograft (Figure 4A) was observed in related vs

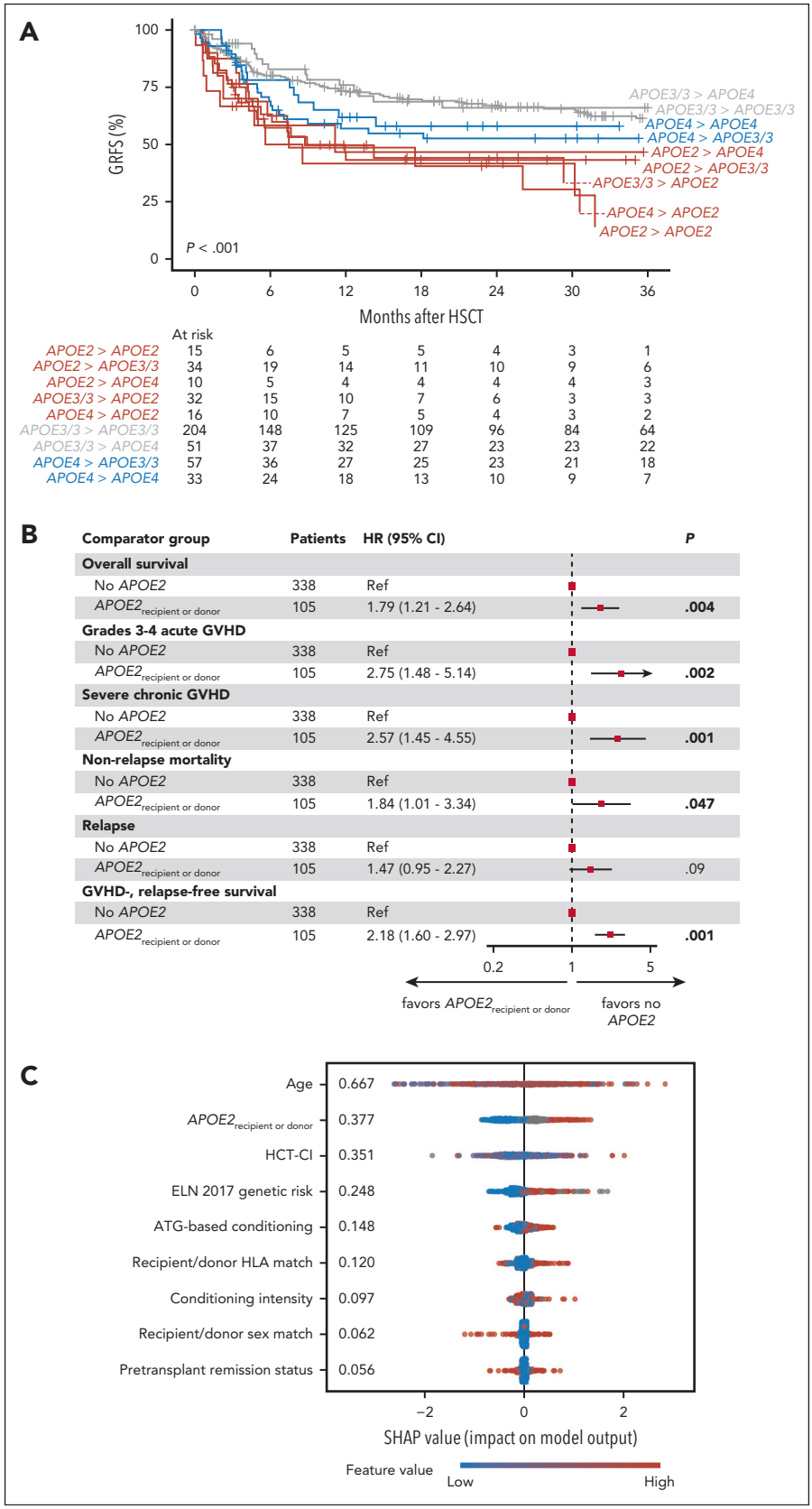

Figure 5. Integration of donor and recipient *APOE* genotype effects on GRFS. (A) GRFS by donor/recipient *APOE* genotype combination. In all constellations listed, the first *APOE* genotype refers to the donor and the second to the recipient. GRFS was compared across all subgroups using a global log-rank test. (B) Forest plot of multivariable adjusted risks for primary and secondary end points, stratified by the presence or absence of the *APOE2* gene in either the host or the allograft. Adjustments were made for patient age, ELN 2017 genetic risk, HCT-CI, pretransplant remission status, ATG treatment, conditioning intensity, recipient/donor HLA match, and recipient/donor sex match.

unrelated donor transplants (eg, *APOE2* carriers receiving an *APOE2*-positive graft, 50% [10/20] in related vs 12% [5/43] in unrelated transplants; $P < .001$; χ^2 test).

OS did not differ by donor *APOE* genotype (*APOE2* vs *APOE3/3*: HR, 1.40; 95% CI, 0.85-2.29; $P = .19$; *APOE2* vs *APOE4*: HR, 1.14; 95% CI, 0.65-2.00; $P = .65$; supplemental Figure 8). Because graft *APOE* genotype is potentially modifiable by donor selection, we next analyzed the effects of donor genotype separately in transplant recipients who carried the *APOE2* risk allele and in those who did not. In *APOE2*-positive patients, donor *APOE* genotype had no further effect on the risk of GVHD development (supplemental Figure 9). In contrast, recipients without an *APOE2* allele who received transplant with *APOE2*-positive allografts were more likely to experience grade 3 to 4 acute GVHD (HR, 2.42; 95% CI, 1.07-5.45; $P = .034$; Figure 4B) and severe chronic GVHD (HR, 2.47; 95% CI, 1.10-5.56; $P = .028$; Figure 4C) than those who received *APOE3* homozygous grafts. The association of *APOE2* allografts with severe acute and chronic GVHD remained significant in multivariable analyses (supplemental Table 7). No significant differences in cumulative incidence of relapse and NRM by donor genotype were observed among non-*APOE2* recipients (Figure 4D-E) or among recipients of all genotypes (supplemental Figure 10). Patients who received transplant from *APOE4*-positive donors showed delayed T-cell reconstitution in the $CD4^+$ compartment, and B-cell counts were reduced in patients with *APOE2*-positive allografts, whereas no difference in natural killer–cell reconstitution was observed (supplemental Figures 11-12).

In theory, the observed effects could be the result of APOE-derived peptides presented on HLA molecules as minor histocompatibility antigens (MiHAs). In this scenario, T cells from donors negative for *APOE2*, and therefore, not tolerant to the *APOE2*-defining rs7412 SNP, could recognize peptides encompassing the relevant SNP in *APOE2*-positive patients, presented by HLA matched between patient and donor (*APOE2* GvH mismatch). This scenario applied to 48 donor-recipient pairs. However, we did not observe a higher risk of GVHD in this subgroup than the 15 pairs without an *APOE2* GvH mismatch (grade 3 to 4 acute GVHD: HR, 0.78; 95% CI, 0.21-2.99; $P = .72$; severe chronic GVHD: HR, 1.24; 95% CI; 0.38-4.07; $P = .72$). Furthermore, in silico prediction of HLA-binding affinities of peptides encompassing rs7412 demonstrated that only the *HLA* alleles B*08:01, B*15:01, and B*51:01, collectively representing ~23% of the population in Germany,[43] showed relevant predicted HLA binding (supplemental Table 8). The incidence of GVHD, however, did not differ between patients with a mismatch at rs7412 who carried at least 1 of the HLA alleles B*08:01, B*15:01, or B*51:01 and those who carried none of these alleles (carriers vs noncarriers; grade 3 to 4 acute GVHD: HR, 0.92; 95% CI; 0.24-3.45; $P = .9$; severe chronic GVHD; HR, 0.88; 95% CI, 0.27-2.85; $P = .83$).

Integrated analysis of *APOE2* effects in donor and host

Because recipient and allograft *APOE* genetic variation differentially affected the risk of relapse, GVHD, and death, we performed an integrated analysis of the combined effects of recipient and donor *APOE* status on the composite end point GRFS, which reflects the major complications of HSCT. Consistent with our findings described above, non-*APOE2* individuals who received grafts from *APOE2* donors were more likely to experience a GRFS event than patients who received transplant from *APOE3/3* donors (*APOE2* vs *APOE3/3* graft: HR, 2.06; 95% CI, 1.32-3.22; $P = .001$; supplemental Figure 13A). In contrast, no donor *APOE* genotype effects on GRFS were observed in *APOE2*-positive recipients (supplemental Figure 13B). When analyzing all recipient/donor genotype combinations, the *APOE2* allele consistently conferred a higher risk of a GRFS event, whether it was present in the recipient or transplanted with the graft ($APOE2_{\text{recipient or donor}}$; Figure 5A). $APOE2_{\text{recipient or donor}}$ remained significantly associated with OS ($P = .004$), acute and chronic GVHD ($P = .002$ and $P = .001$, respectively), NRM ($P = .047$), and GFRS ($P < .001$) after multivariable adjustment (Figure 5B; supplemental Tables 9-10).

Finally, we used the *XGBoost* algorithm, a gradient boosting ensemble of decision trees widely used for classification tasks, to understand the relative importance of the *APOE2* allele among other clinicopathological variables on GRFS. When potential drivers of risk for a GRFS event were quantified using the *SHAP* framework, $APOE2_{\text{recipient or donor}}$ was among the most influential features, ranking second only to patient age and above established risk features, including AML genetic risk and recipient/donor HLA or sex matching (Figure 5C).

Discussion

Although the link between *APOE* germ line variation and cognitive impairment has long been established, its role in immune regulation and antitumor immunity has only recently been recognized.[4,5,24] Our study is, to our knowledge, the first to examine the impact of common hereditary *APOE* variants in the context of allogeneic HSCT. We identify *APOE2*, which is otherwise associated with longevity and a reduced risk of dementia and cardiovascular events,[20,22,44] as a germ line risk allele for posttransplant complications in AML, when carried by the patient or when transferred by the graft from *APOE2*-positive donors. The potential clinical impact of our findings is significant, given the high prevalence of the *APOE2* allele in up to 15% of the general population and the availability of risk-reduction strategies, such as individualized GVHD prophylaxis or, ultimately, personalized donor selection.

Several potential mechanisms may be at the basis of our findings. The *APOE2*-encoded protein differs from the other 2 variants due to the amino cysteine at positions 112 and 158,[16] resulting in

Figure 5 (continued) (C) SHAP beeswarm plot for prediction of GRFS with *XGBoost*. GRFS was binarized at the 12-month landmark, and patients censored before 12 months of follow-up (n = 149) were excluded. Automatically selected input features are ranked from most influential (top) to least influential (bottom). Dots represent individual patients. On the x-axis, SHAP values indicate the magnitude and direction of how a feature affects the final prediction of a GRFS event in the first year after HSCT. Age and HCT-CI were treated as continuous variables, with higher feature values (red) representing older patients or higher HCT-CI scores, respectively. All other variables were categorical, and red dots indicate *APOE2* positivity (in host or allograft), adverse genetic risk, no ATG treatment, HLA mismatch, myeloablative conditioning, donor sex mismatch (male recipient/female donor), and CRi before HSCT, respectively. Features are sorted on the y-axis according to their importance. We provide SHAP values for the model with average values of 100 runs.

poorer binding to lipoprotein surface receptors.[45,46] It is tightly linked to hereditary type III hyperlipoproteinemia, in which it is homozygous in >90% of affected individuals.[47,48] The associations we describe with allogeneic HSCT outcomes raise the intriguing hypothesis of a role for lipid metabolism in the complex immunological mechanisms associated with this treatment, in line with recent evidence from others.[49,50] Notably, the *APOE* locus on human chromosome 19q13.32 is proximal to the polymorphic *killer immunoglobulin-like receptor (KIR)* gene locus on 19q13.4. Extensive research to associate *KIR* variability with HSCT outcomes has yielded conflicting and inconclusive results.[51-54] In our study, we found no effect of donor or recipient *APOE* genotype on natural killer–cell reconstitution. Further analysis, for example, correlation with donor-recipient *KIR* genotypes, might help elucidate this issue, although it is beyond the scope of this study. In addition, *APOE* isoforms have been shown to differentially influence the gut microbiome,[55] which in turn has been implicated in the development and severity of GVHD.[56-58] Finally, mismatched APOE-derived peptides could theoretically be presented as MiHAs on HLA class I molecules, triggering alloreactive T-cell responses. However, we observed adverse *APOE2* effects even in transplant recipients with no disparity at the rs7412 locus, suggesting that *APOE2* isoform effects are more likely to be explained by biological function rather than by HLA presentation and T-cell recognition of mismatched peptides. The observation that *APOE2* grafted from a positive donor into a negative patient was also associated with increased GVHD further argues against patient APOE2-derived MiHAs as the primary mechanistic explanation for our findings. Finally, no APOE variants were not identified in a recent comprehensive analysis of the dominant repertoire of HLA class I–restricted MiHAs.[59,60]

Several studies have shown that APOE may act as a mediator of antigen presentation and T-cell activation with isoform-specific effects,[4-6,26,61] yet its role in immune regulation is complex and not fully understood. This is even more true in the setting of stem cell transplantation, in which donor-derived hematopoietic *APOE* adds an additional layer of complexity. Nevertheless, our findings show parallels with previous studies investigating immune effects of *APOE* isoforms in other disease contexts. In COVID-19, in which *APOE2* and *APOE4* alleles were associated with decreased survival in mouse models, both *APOE2* and *APOE4* transgenic mice showed suppressed adaptive immune responses early after infection, but *APOE4* mice generated robust antiviral T-cell immunity at later disease stages.[6] Mirroring this, *APOE4*-positive allografts were linked to a lower risk of acute GVHD and delayed immune reconstitution early after transplantation.

There are limitations to the interpretation of our results. First, our study is retrospective in nature, and therefore, our findings should be interpreted as associative rather than proving a cause-and-effect relationship. Second, although we were able to obtain consistent results in the discovery and an independent validation cohort, the numbers in the *APOE2* and *APOE4* subgroups in each of them are still limited, especially in the subcohort with available donor genotype. Therefore, it is important to emphasize that it would be premature to draw firm conclusions regarding the selection of stem cell donors. Third, given the low prevalence of *APOE2* or *APOE4* homozygosity in our leukemia cohorts, similar to the general population, it remains unclear whether there is a gene dose effect. Future efforts may define a more nuanced understanding of the impact of donor *APOE* genotype and zygosity on HSCT outcomes, using at least high 4-digit sample sizes and more geographically diverse, multiancestry cohorts. Fourth, it remains to be shown whether our results can be generalized to patients receiving HSCT for indications other than AML, although we observed that *APOE* genotype was primarily linked with common procedural complications of HSCT. Similarly, further studies are needed to investigate whether our findings are applicable in the context of posttransplant cyclophosphamide–based GVHD prophylaxis, given the limited number of patients in this study. For this reason and others, we acknowledge that it remains uncertain whether our observations are relevant to transplant settings outside of Germany or Europe. Fifth, we focused our genotyping efforts on the 2 most common polymorphisms. Our study does not provide information on the potential impact of rare *APOE* variants, such as Christchurch (R136S) or Jacksonville (V236E), which have been shown to be protective against Alzheimer disease.[62,63] Finally, because the *APOE* genotype provides information on the risk of neurodegenerative and cardiovascular diseases, knowledge of the results of genetic susceptibility testing may cause emotional distress. In a prospective randomized trial of the effects of *APOE* genotype disclosure to adult children of patients with Alzheimer disease, patients who learned that they were *APOE4* positive did not show more anxiety, depression, or test-related distress than those who did not learn their genotype.[64] However, how disclosure of genotyping results would affect patients who are evaluated for transplantation or their family donors needs to be studied.

Within these constraints, we provide, to our knowledge, the first evidence that the inherited *APOE2* variant of the *APOE* gene, in recipients or donors, is associated with adverse outcome after allogeneic HSCT. A better understanding of how recipient-donor *APOE* genotype interactions cause posttransplant complications could lead to *APOE* genotype–guided risk stratification, tailored immunosuppressive strategies, as well as more informed donor selection.

Acknowledgments

The authors thank all patients and their families who contributed data to our research. The authors highly appreciate the help of all nurses, data managers, and physicians of all contributing HSCT centers, and they thank Gerburg Nettels-Hackert and Irina Arnhold for their technical support.

J.R. is supported by grants from the Innovative Medical Research Fund (grant RO212301) by the University of Münster and the Circle of Friends of the Bone Marrow Transplantation Unit Münster. B.N.O. is supported by a Max Eder grant of the German Cancer Aid (reference 70114327) and is a fellow of the Digital Clinician Scientist Program at Berlin Institute of Health-Charité. S.F.T. was supported by U54CA261701 and R35CA274446 awards from the National Cancer Institute, National Institutes of Health, as well as the Black Family Metastasis Center and the Breast Cancer Research Foundation. C.S. is supported by a grant from the José Carreras Leukaemia Foundation (DJCLS05R/2022). Analyses on UK Biobank participants were conducted using the UK Biobank Resource under application number 62709. Molecular graphics and analyses performed with University of California, San Francisco ChimeraX, developed by the Resource for Biocomputing, Visualization, and Informatics at the University of California, San Francisco, with support from the National Institute of General Medical Sciences, National Institutes of Health (grant R01-GM129325) and the Office of Cyber Infrastructure and Computational Biology, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

The graphical abstract was created, in part, with BioRender.com.

Authorship

Contribution: J.R., M.S., and C.S. conceived and designed the study; M.K., C.K., H.B., S.A., F.T.F., A.S., H.S., B.S., and J.S. provided administrative support; J.R., M.G., C.K., H.B., A.F.B., S.S., L.K., P.B., B.N.O., and S.F.T. collected the data; J.A., C.R., S.C., J.M., M.F., E.E., J.-H.M., W.E.B., G.L., M.S., and C.S. contributed to patient management; J.R., M.G., K.F., M.S., and C.S. analyzed and interpreted the data; and all authors provided access to primary data, wrote the manuscript, approved the manuscript, and are accountable for all aspects of the work.

Conflict-of-interest disclosure: J.R. received travel support not related to this manuscript from AbbVie. A.F.B. received speaker honoraria not related to this manuscript from AbbVie. W.E.B. is equity holder of Anturec Pharmaceuticals and Elvesca Biotherapeutics; and has stock options in Philogen. J.-H.M. received honoraria not related to this manuscript from Pfizer, Daiichi Sankyo, Delbert Lab, Otsuka, Alexion, GlaxoSmithKline, Servier, Bristol Myers Squibb, Pfizer, Celgene, Novartis, Jazz Pharmaceutics, BeiGene, Servier, and Astellas; and congress support from Alexion, Astellas, Pfizer, Celgene, Jazz Pharmaceutics, Novartis, and Servier. G.L. received research grants not related to this manuscript from AGIOS, AQUINOX, AstraZeneca, Bayer, Celgene, Gilead, Janssen, MorphoSys, Novartis, F. Hoffmann-La Roche Ltd, and Verastem; and also received honoraria not related to this study from ADC Therapeutics, AbbVie, Amgen, AstraZeneca, Bayer, BeiGene, BMS, Celgene, Constellation, Genase, Genmab, Gilead, Hexal/Sandoz, Immagene, Incyte, Janssen, Karyopharm, Lilly, Miltenyi, MorphoSys, Merck Sharp & Dohme, NanoString, Novartis, PentixaPharm, Pierre Fabre, F. Hoffmann-La Roche Ltd, and Sobi. J.S. received honoraria not related to this manuscript from AbbVie, Astellas, AstraZeneca, BeiGene, BMS, Eurocept, Janssen, Medac, MSD, Novartis, and Sanofi. M.S. received grants not related to this manuscript from Pfizer; and also received honoraria not related to this manuscript from Pfizer, Jazz, Amgen, Novartis, Gilead, Celgene, medac, BMS, MSD, and Incyte. C.S. received institutional research support not related to this manuscript from Jazz Pharmaceuticals; received honoraria not related to this manuscript from AbbVie, Astellas, AstraZeneca, BMS, Laboratories Delbert, Jazz Pharmaceuticals, Novartis, Otsuka, Pfizer, and Roche; and travel grants from AbbVie, BMS, Jazz Pharmaceuticals, and Pfizer. The remaining authors declare no competing financial interests.

ORCID profiles: J.R., 0009-0006-1955-0709; M.G., 0000-0003-1909-0133; M.K., 0009-0007-1424-2165; A.F.B., 0000-0002-7120-2780; S.S., 0000-0002-5011-0641; M.F., 0009-0005-0916-070X; L.K., 0009-0001-4850-7359; P.B., 0000-0002-4152-0366; K.W., 0000-0002-1899-3261; W.E.B., 0000-0002-3030-6567; B.N.O., 0000-0003-4492-9252; K.F., 0000-0002-5827-8000; J.S., 0000-0002-2780-2981; C.S., 0000-0003-1755-9583.

Correspondence: Christoph Schliemann, Department of Medicine A, University Hospital Münster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany; email: christoph.schliemann@ukmuenster.de.

Footnotes

Submitted 10 September 2024; accepted 5 January 2025; prepublished online on *Blood* First Edition 15 January 2025. https://doi.org/10.1182/blood.2024026886.

Presented in part at the 2024 annual meeting of the European Hematology Association, Madrid, Spain, 13 to 16 June 2024.

The data that support the findings of this study are available from the corresponding author, Christoph Schliemann (christoph.schliemann@ukmuenster.de) upon reasonable request.

The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

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